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OFFICE OF NAVAL RESEARCH  
ANNUAL PROGRESS REPORT

Report prepared by: José M. R. Delgado, M.D.

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CONTRACTOR: Yale University

PRINCIPAL INVESTIGATOR: José M. R. Delgado

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TITLE OF PROJECT: Neurological Mechanisms in epilepsy and behavior

- Objectives:
- a) The investigation of the possible roles of different cerebral structures in epileptic phenomena.
  - b) The study of the site of action of CO<sub>2</sub>, O<sub>2</sub>, and antiepileptic and tranquilizing drugs.
  - c) The study of cardiovascular phenomena under cerebral control.
  - d) To analyze the neurophysiological basis of behavior by means of intracerebral stimulation in monkeys, completely free within a colony.

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ABSTRACT (OR SUMMARY) OF RESULTS

A. Since Start of Project: See annual reports for 1954 through 1960.

B. During current report period

Methods for remote controlled stimulation of the brain described in the literature are unreliable, mainly because intensity of stimulation changes if the orientation of the receiving antenna is modified by animal movements. Also, the monitoring of stimulation is often difficult. These problems, as well as others, seem to be solved by a new method for electrical stimulation of the brain, controlled by radio, which we have developed during the present report period.

In collaboration with Drs. Bucaille, Spiro and de los Santos, a program has been started to study cerebral-gastrointestinal correlations. In a group of seven monkeys, cannulas were permanently implanted in the stomach, and multilead electrodes permanently implanted in the brain. Some of the control studies, as well as the reactions after histamine injection seemed to indicate that gastrointestinal functions in the Macaca Mulatta are similar to those in human beings, and different from those in other experimental animals, such as cats and dogs. Electrical stimulation of a few points within the frontal lobe was able to modify acidity and gastric pressure, while stimulation of many other areas was ineffective, suggesting that the areas which influence gastrointestinal function are rather localized.

The study of aminophenylpyridone was continued with a derivative named Carbomethoxy-aminophenyl-pyridone, which produces interesting behavioral disassociation with simultaneous drowsiness and increased aggressiveness. Considerable modification of the electrical activity of the brain was recorded over a wide area of the cerebral

cortex, while the activity was only slightly modified in some of the limbic structures.

In collaboration with Dr. Paudler, from Wright-Patterson Airfield Base, a boron compound has been administered to a group of ten monkeys. Data are at present being processed to evaluate possible changes in electrical activity and excitability, and also possible modifications of behavior.

The study of the cerebral structures which influence social behavior in the monkey was continued, and a large amount of data is being analyzed at present.

In addition, the following research has been completed and published:

1. Electroencephalography of the deeper cell masses of the brain. This is a chapter of a book edited by Schaltenbrand and Bailey, and published simultaneously in German and in English. Methods of implanting electrodes in human beings are described. Indications of the procedure are discussed, mentioning also the possible risks and the results of the study of several patients are presented, showing the electrical activity recorded in different parts of the brain in schizophrenics and epileptics.
2. Effect of amphenidone on the brain of the conscious monkey. Under the trade name of Dornwal, amphenidone has been introduced recently into clinical practise as a tranquilizer. This paper studies the effect of amphenidone on the brain. Six monkeys with permanently implanted intracerebral electrodes were used, and two others were employed in acute experiments. Local application of amphenidone decreased the excitability of the motor complex. Oral and intravenous administration of 100 mg/kg of the drug increased afterdischarge thresholds and decreased duration of seizures evoked by stimulation of motor cortex, thalamus and septum. In one monkey, the motor cortex was more depressed by 100 mg/kg of amphenidone than by 15 mg/kg of phenobarbital, but excitability

of the amygdala was only slightly affected. Amphenidone generally caused an increase in slow wave activity in motor cortex, thalamus and septum, with little or no effect on the amygdala. Oral administration caused mild sedation and lessened aggressiveness, but produced no drowsiness. No untoward effects were observed.

3. Cardiovascular phenomena during seizure activities. Epileptic attacks are very often accompanied by cardiovascular alterations such as flushing of the face, increase in blood pressure and modification of heart rhythm. In visceral seizures some of these symptoms may be the principal manifestations of illness. In the present investigation, correlations between seizure activity and cardiovascular phenomena were analyzed in ten rhesus monkeys, six cats and nine patients. Results were as follows:

Electrical stimulation of some points of the motor cortex (cat), subiculum, posterior hippocampus and substantia nigra (monkey) produced cardiovascular effects, without any alteration in the spontaneous electrical activity of the brain.

Electrical stimulation of the orbital cortex (cat), central gray, fornix (monkey) and temporal lobe (human) produced cardiovascular effects only if intensities strong enough to evoke afterdischarges were used.

Afterdischarges localized in the thalamus, substantia nigra (cat), motor cortex, amygdala, thalamus (monkey), orbital cortex (human) were not accompanied by cardiovascular manifestations.

The above-mentioned results show that cardiovascular effects may be evoked without disturbance of the electric activity of the brain, and seizure activity may exist in the absence of cardiovascular reactions--proving the independence of both phenomena.

4. Circulatory effects of cortical stimulation. The literature concerning the circulatory effect of cortical stimulation is reviewed in Part I of this paper, and experimental material is presented in Part II. In our studies the brain was stimulated through implanted electrodes without anesthesia, chemical immobilization or restraint, which have been handicaps in previous investigations. The cortical areas with cardiovascular function are located in the anterior part of the brain, and include the tip of the frontal lobe, the orbital cortex, the motor cortex, the hidden motor areas, the anterior part of the temporal lobe, the insula and the cingulate gyrus.

Cardiovascular representation is discontinuous. Direction, magnitude, latency, fatigue, and reliability of the phenomena are characteristic of the evoked effects. Conflicting results reported in the literature can be explained as the result of uncontrolled experimental variables which include homeostatic mechanisms, anesthesia, and physical characteristics of the stimulation.

Our experiments have been carried on in monkeys, cats and humans. In the cat, in addition to intracerebral electrodes, a permanent intraarterial cannula was implanted in order to record the blood pressure electrically in the absence of anesthesia and restraint. We have shown that: 1) The hidden motor cortex of the cat has cardiovascular representation. 2) Autonomic and somatic effects may be evoked independently, suggesting a separate cortical representation. However, both effects were often related anatomically and functionally. 3) Specificity of representation was demonstrated by the fact that electrical stimulation of different structures of the brain could modify selectively the heart rate, evoke ectopic atrial beats, produce ventricular extrasystoles, or alter the blood pressure.

4) Electrical stimulation of one cerebral point evoked seizure activity in areas located many millimeters distant, and further investigation is needed to learn which region is responsible for the evoked effect. 5) Cardiovascular effects faded away in spite of the continuous cerebral stimulation. 6) Cerebral structures may be classified according to the effect of stimulation in areas which modify the heart function without producing disturbances in the electrical activity of the brain: areas which do not affect cardiac function even during paroxysmic discharges; and areas which influence the heart during seizure activity but not at subthreshold levels of stimulation.

5. Behavioral correlates of limbic afterdischarge in the monkey. General behavior, reactions to food and fear stimuli, and conditioned avoidance responses were studied in two monkeys during electrically evoked hippocampal afterdischarges (HAD). The animals were observed on a 6' x 2' training platform, and continuous depth EEG and EKG recordings were made. Conditional avoidance testing of the monkeys included auditory and visual plus go-no-go and two choice responses. Results were as follows: 1) learned responses were diminished during HAD, but not following subthreshold stimulation of the hippocampus; 2) there was a quantitative and qualitative difference between the deficits produced by unilateral and by bilateral HAD; 3) escape responses to shock were not modified by unilateral HAD, but were disturbed by bilateral HAD; 4) emotional reactivity and expression were normal during unilateral HAD, but were reduced or absent during bilateral HAD; 5) normal conditioned responses reappeared as soon as HAD ceased; 6) EKG responses to the conditioned stimulus were absent when the animals failed the behavioral response; 7) HAD produced few EKG changes, but marked bradycardia followed the end of the seizure.



6. Emotional behavior in animals and humans. Emotional behavior may be induced in cats and monkeys by electrical stimulation of the brain. Experimental evidence suggests that cerebral structures studied can be classified in three groups: 1) unrelated to emotions: motor cortex, pulvinar, substantia nigra; 2) related to external behavioral manifestation of emotions but not to emotional experience: hypothalamus; 3) related to both behavioral manifestation and emotional experience: part of the hippocampus, postero-ventral nucleus of the thalamus, tectal area. Conditioning may be induced by electrical stimulation of structures of the last group, but not by the first two.

Evoked fear-like responses did not fatigue for 15 minutes, in contrast to motor responses evoked by stimulation of pre-central cortex which fatigued in a few seconds.

The following types of inhibited behavior were evoked in monkeys by electrical stimulation of specific areas: 1) inhibition of motor behavior, 2) dozing, 3) arrest reaction, 4) hypotonic reaction, 5) specific inhibition of aggressiveness, 6) specific inhibition of interest in food.

Objective and subjective manifestation of friendliness, pleasure and fear were evoked in conscious patients by electrical stimulation, proving that experiential and expressive aspects of emotion can be artificially induced by excitation of specific cerebral structures.

7. Neurophysiological basis of effective behavior. In the investigation of the psychic life of animals, it is difficult to study their sensations because animals do not speak and cannot communicate their feelings. Investigators usually study only the expressive side of the emotion, observing and recording motor and autonomic manifestations, and deducing by

comparison the possible affective state. One way to understand the complex system of communication of animals expressed through vocalization, mimicry, gestures and postures is to analyze social behavior with one animal reacting to the expressions of another. Methodological advances which we have developed for this type of study are presented in this paper. This includes the use of multilead electrodes with contacts on the surface and depth of the brain, transistorized portable stimulators with programming mechanism carried by the animal around the neck, the use of subcutaneous leads which it cannot break, the implantation of subcutaneous sockets with minute mercury wells located in a very small piece of lucite and covered by rubber, and the use of time-lapse photography to record social behavior.

Cerebral structures are divided into several groups according to their participation in conscious perception and in external psychic manifestations. Experimental data are given to demonstrate that some structures participate in both; some others participate only in the external manifestation of the emotions, without conscious perceptions; some other areas do not participate in emotional behavior; and still another group of structures have an inhibitory effect.

8. Brain and social behavior in the monkey. The purpose of this film is to demonstrate techniques to quantify social behavior of monkeys and to study modifications induced by drugs and by brain stimulation. The first part explains the methods used: (i) to record social behavior by time-lapse photography, (ii) to analyze and quantify the records by means of a time-study projector, electric typewriter, and electronic computer, and (iii) to program stimulation of the animals with tiny transistor-stimulators carried on

a collar and connected to the brain through subcutaneous leads. The second part of the film shows quantification of 24 categories of daily behavior. Administration of chlorpromazine, reserpine, iproniazid, pentobarbital and estradiol modify the quality and quantity of behavioral categories. Stimulation of central gray increases the aggressiveness of the stimulated monkey and produces social spread of attacking behavior. Stimulation of the nucleus anterior ventralis of the thalamus evokes running away and hiding. Histological study shows that prolonged stimulation of the brain does not alter the neurons.

9. Spontaneous and evoked electrical seizures in animals and in humans. Our experience in the study of the unanesthetized brain, based upon research of the last ten years in about 100 cats, 100 monkeys and 30 human patients with intracerebral electrodes, supports the following conclusions:

1. In humans the use of implanted electrodes offered the following advantages over open surgical exploration: no anesthesia; less trauma; wide coverage of the surface and depth of the brain; exploration of areas of difficult surgical access, such as the inferomedial portion of the temporal lobe; prolonged observation time and repetition of exploration without environmental stress.

2. In general, insertion of depth electrodes produced histologic changes of negligible electroencephalographic or functional significance. Rigid electrode arrays, however, might produce local irritation.

3. Paroxysmal activity has been observed in different types of non-epileptic patients, and great caution is advised in applying scalp recording experience to the interpretation of direct recordings.

4. The cerebral electrical field that influences the contacts in direct bipolar recordings is only a few millimeters in extent. Study of tracings, therefore, has localization value.

5. Within the limbic system of the monkey electrical stimulation of different points evoked afterdischarges, mainly in the area of lowest threshold, which was the anterior hippocampus. The pattern of the afterdischarge was similar in all cases. Study of local patterns of afterdischarge, therefore, may have a localizing value with respect to position of electrodes and the cerebral system involved in different types of seizures.

6. Sensation of pleasure, friendly verbalization modification of sexual drive, and déjà vu have been evoked by electrical stimulation of the temporal lobes in epileptic patients. Psychological and electroencephalographic correlation was found in some cases.

7. Spontaneous attacks in epileptics showed electrical patterns with typical characteristics in space and time that recurred during different attacks. The pattern in each linkage seemed to be the result of the interrelation of a general pacemaker and local factors. Study of local patterns may have anatomic, functional, and physiopathologic value.

## PLANS FOR THE FUTURE

A. Immediate: (a) Our present radio-controlled cerebral stimulator has only one channel, and we are planning to improve its circuitry; to have two or more channels, and, at the same time, to reduce weight and size. (b) The study of cerebral-gastro-intestinal correlations will be expanded, and the preparation of monkeys with gastric pouches is contemplated. (c) Modification of social behavior by remote-controlled stimulation of the brain, and its recording by time-lapse photography, has already given very interesting results. Cats and monkeys will both be used in future studies, grouped in separate colonies. In the more remote future, chimpanzees could be studied. (d) The investigation of the functions of different cerebral structures during epileptic phenomena will be continued in monkeys.

B. Long-range: The above-mentioned plans include the long-range plans for the future.

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